(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 03/106447 A1

(51) International Patent Classification[7]: C07D 319/06

(21) International Application Number: PCT/NL03/00435

(22) International Filing Date: 12 June 2003 (12.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02100715.8 17 June 2002 (17.06.2002) EP

(71) Applicant *(for all designated States except US)*: **DSM IP ASSESTS B.V.** [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BAKEL VAN, Hermanus, Carolus, Catherina, Karel** [NL/NL]; Barbarastraat 10, NL-5988 BC Helden (NL). **CALLANT, Dominique, Monique, Charles** [BE/BE]; De Huttestraat 93, B-3530 Houthalen (BE). **KOOISTRA, Jacob, Hermanus, Mattheus, Hero** [NL/NL]; Gaspeldoornstraat 32, NL-5925 BA Venlo (NL). **MAAS, Peter, Johannes, Dominicus** [NL/NL]; Geleenstraat 70, NL-6155 ND Puth (NL).

(74) Agent: **JACOBS, Monique, Sophie, Nicole**; DSM Intellectual Property, P.O. Box 9, NL-6160 MA Geleen (NL).

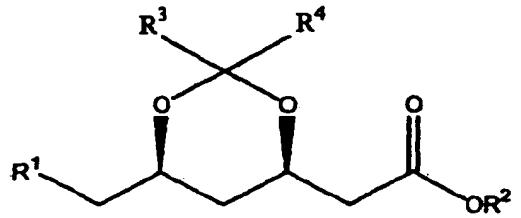
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

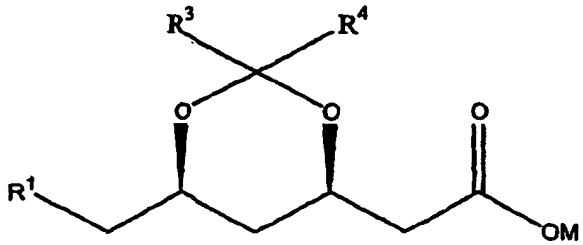
Published:
— *with international search report*

[Continued on next page]

(54) Title: PROCESS FOR THE PREPARATION OF DIOXANE ACETIC ACID ESTERS



(1)



(2)

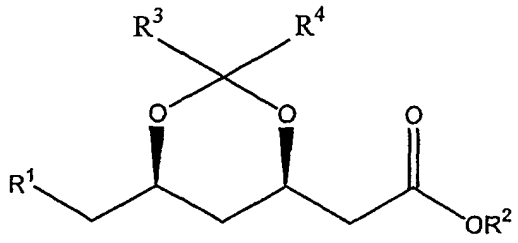
(57) Abstract: Process for the preparation of an ester of formula (1), wherein R^1represents a leaving group, CN, OH or a $COOR^5$ group, R^3 and R^4each independently represent a 1-3 C alkyl group, and R^2 and R^5 each independently represent an ester residue, wherein the corresponding salt with formula (2), wherein M represents H or an alkali (earth) metal in an inert solvent is contacted with an acid chloride forming agent to form the corresponding acid chloride, and the acid chloride is contacted with an alcohol with formula R^2OH in the presence of N-methyl-morpholine. Preferably M represents an alkali metal, and R^2 represents an alkyl group, particularly a t.-butyl group. (1), (2)

WO 03/106447 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

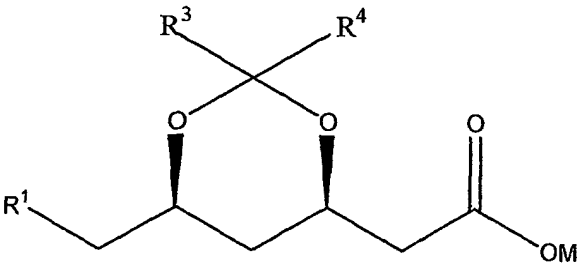
PROCESS FOR THE PREPARATION OF DIOXANE ACETIC ACID ESTERS

The invention relates to a process for the preparation of an ester of formula (1)



(1)

wherein R^1 represents a leaving group, CN, OH or a $COOR^5$ group, R^3 and R^4 each independently represent a C1-3 alkyl group and R^2 and R^5 each independently represent an ester residue, wherein the corresponding salt with formula (2)



(2)

wherein M represents H or an alkali (earth) metal in an inert solvent is contacted with an acid chloride forming agent to form the corresponding acid chloride, and the acid chloride is contacted with an alcohol with formula R^2OH in the presence of N-methyl morpholine (NMM).

Many processes for the preparation of esters are known in the art, for instance the preparation of esters via the formation of the acid chloride. It was, however, to be expected that such processes would not lead to high yields due to the lack of stability of the present compound under acidic conditions.

It is the object of the invention to provide a process for the

preparation of esters with high yield in a robust process, even at large scale and with relatively high concentrations.

Surprisingly it has been found that even sterically hindered esters that are difficult to obtain in esterifications like t-butyl esters of the acid unstable molecules of formula (1), can be obtained in high yield in an easily reproducible process.

With the process according to the invention esters with formula (1) that are unstable under acidic conditions, for instance with pH < 4, can be prepared in high yield.

R^1 represents a leaving group, CN, OH or a $COOR^5$ group wherein R^5 represents an ester residue, for example an alkyl group with for instance 1-6 C-atoms, or an aryl group with for instance 6-12 C-atoms. A leaving group by definition is a group that can easily be replaced, for example a halogen, for instance Cl, Br or I; a tosylate group; a mesylate group; an acyloxy group, with, for instance, 1-6 C-atoms in particular an acetoxy group; a phenacetyloxy group; an alkoxy group with, for instance, 1-6 C-atoms or an (hetero) aryloxy group with, for instance, 6-12 C-atoms . Preferably R^1 represents Cl.

R^2 represents an ester residue, preferably an alkyl group, for instance an alkyl group with 1-6 C-atoms or an aryl group, for instance an aryl group with 6-12 C-atoms, in particular a methyl, ethyl, propyl, isobutyl or t.butyl group. An important group of esters that can be prepared with the process according to the invention are t.butyl esters.

R^3 and R^4 each independently represent a C1-C3 alkyl group, for instance a methyl or ethyl group. Preferably R^3 and R^4 both represent methyl.

M in formula (2) can be chosen from the group of H, alkali metals, for instance lithium, sodium, potassium and alkali earth metals, for instance magnesium or calcium. Preferably M represents sodium or potassium.

The acid chloride forming agent can be chosen from the group of reagents that is generally known as such. Suitable examples of acid chloride forming agents are oxalyl chloride, thionyl chloride, PCl_3, PCl_5, and $POCl_3$. Preferably the acid chloride forming agent is used in an excess relative to the amount the salt with formula (2), for instance between 1 and 3 equivalents, more preferably between 1.2 and 1.8 equivalents.

If desired, in the acid chloride formation also a catalyst may be present. The amount of catalyst may for instance vary from 0-1, preferably 0-0.5 equivalents, calculated with respect to the amount of salt with formula (2). Higher

amounts of catalyst are also possible, but will normally have no extra advantageous effect. Preferably the amount of catalyst, if any, will be between 0.05 and 0.2 equivalents calculated with respect to the salt with formula (2).Suitable catalysts are the catalysts generally know to accelerate acid chloride formation, for instance dimethylformamide (DMF) and N-methylpyrrolidone (NMP).

The conversion of the acid chloride into the ester with formula (1) is carried out in the presence of an alcohol with formula R^2OH. The amount of alcohol with formula R^2OH is not very critical and preferably is between 1 and 15 equivalent calculated with respect to the amount of salt with formula (2), more preferably between 2 and 13, most preferably between 3 and 6. Surprisingly it has been found that even t.-butyl esters can be prepared with high yield using a relatively low amount of t.-butyl alcohol.

The conversion of the acid chloride into the ester with formula (1) is carried out in the presence of NMM. In practice a small amount of NMM, efficient to catch eventually remaining free HCl, for instance 1.5 to 2.5, preferably 1.8 to 2.0 equivalents calculated with respect to the amount of salt with formula (2) is applied. When a large excess of acid chloride forming agent is used, preferably higher amounts of NMM are used, and when a lower excess of acid chloride forming agent is used, preferably lower amounts of NMM are used.

The acid chloride formation reaction preferably is carried out at a temperature between -30° and 60°C, more preferably between 20 and 50°C. The conversion of the acid chloride into the ester with formula (1) preferably is carried out at a temperature between 20 and 80°C, more preferably between 20 and 50°C.

The process of the present invention may be carried out in one step. Preferably first the salt with formula (2) is converted into the corresponding acid chloride, and subsequently the acid chloride is contacted with the alcohol with formula R^2OH and NMM. In a particularly preferred embodiment the acid chloride formed is quenched with NMM and the alcohol with formula R^2OH.

The product with formula 1, wherein R^1 represents a leaving group may subsequently be converted into the corresponding compound wherein R^1 represents an acyloxy group. This can be achieved in a manner known per se, for instance by reaction with an acyloxylating agent for instance a carboxylic or sulphonic acid, a quaternary ammonium or phosphonium salt, a carboxylic or sulphonic acid quaternary ammonium or phosphonium salt or a combination thereof. Preferably a combination of a quaternary phosphonium salt and a carboxylic or sulphonic acid salt is used as the acyloxylating agent.

Subsequently the compound with formula 1, wherein R^1 represents an acyloxy group can be converted in the corresponding compound wherein R^1 represents a hydroxy group, for instance by subjecting it to solvolysis in the presence of a base. Suitable bases are, for instance, alkali (earth) metal hydroxides or carbonates or organic bases, for instance alkali (earth) metal carboxylic acids, for instance acetates, ammonia, pyridines, amines, for instance triethylamine and the like.

The invention will be elucidated by the following examples.

Example I

1864 g of an aqueous solution of the (4R-cis)-(6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetic acid, sodium salt (3.31 moles) and 4.8 L of toluene were mixed and water was removed by azeotropic distillation under reduced pressure. Subsequently, 870 g of fresh toluene were added and removed by distillation. To the obtained suspension was added 33.4g of NMP. Then 588 g of oxalyl chloride were added while maintaining the temperature at 20 °C. The resulting mixture was stirred for 6 hours at 20-25 °C and then slowly added to a mixture of 979 g of t.-butanol and 836 g of *N*-methyl morpholine. After stirring for 1 hour, 3966 g of an 8% (w/w) aqueous NaOH solution was added and the resulting mixture stirred for 1.5 hours at 40 °C. After washing the organic phase with 3300 g of water, 3064 g of a toluene solution of the desired t.-butyl ester was obtained, corresponding to 751 g (81%) of product.

Example II

In a 100 ml HEL Vessel with 4 blade stirrer 8.0 g (4R-cis)-(6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetic acid, sodium salt (92.4%; 30 mmol) was suspended in 41 g toluene and 0.3 g NMP (3 mmol). In 1h 4.5 g (36 mmol) oxalylchloride was dosed at a temperature of 15-20°C. The reaction mixture (50 g) was stirred for 2.5 hours. The reaction mixture was split into 2 parts: Part A (23.83 g) and part B (24.25 g). Part A of the reaction mixture was dosed during 1 h. to a mixture of 22.2 g (20 eq.) t.-butanol and 3.0 g (2 eq.) NMM at 25°C. The reaction mixture was stirred overnight and analyzed by GC. The yield of the t.-butyl ester was 88%.

Examples III-V

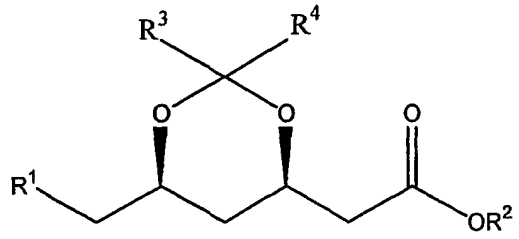
Following the same procedure as described in Example I, the ethyl, isopropyl and n-hexyl esters, respectively, are prepared wherein instead of 4 eq. butanol, now 4 eq. ethanol, 4 eq. isopropanol and 4 eq. n-hexanol, respectively is used. The yield of the desired ethyl, isopropyl and n-hexyl ester was 89 mol%, 88 mol% and 84 mol% respectively, calculated with respect to the sodium salt starting material.

Example VI

A mixture of 35.0 g of t-butyl (4R-cis)-(6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetate, 14.8 g of tetrabutyl phosphonium bromide, 16.0 g of potassium acetate and 5.9 g of toluene were heated to 105 °C under reduced pressure. After 22 hours at this temperature the reaction mixture was cooled to ambient temperature after which 400 g of heptane and 350 g of water were added. The organic phase was washed with 150 g of water and subsequently treated with 3.0 g of activated carbon. After filtration of the carbon, the solution was concentrated and subsequently cooled to -10 °C after which crystallised product was isolated by means of filtration. Yield 24.9 g (76%) of a white crystalline material

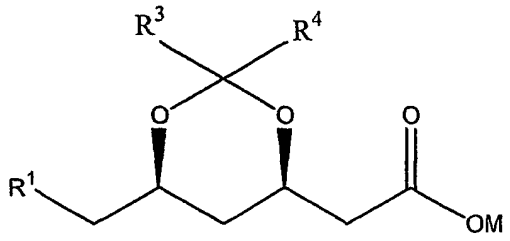
CLAIMS

1. Process for the preparation of an ester of formula (1),



(1)

wherein R^1 represents a leaving group, CN, OH or a $COOR^5$ group, R^3 and R^4 each independently represent a 1-3 C alkyl group, and R^2 and R^5 each independently represent an ester residue, wherein the corresponding salt with formula (2),



(2)

wherein M represents H or an alkali (earth) metal in an inert solvent is contacted with an acid chloride forming agent to form the corresponding acid chloride, and the acid chloride is contacted with an alcohol with formula R^2OH in the presence of N-methyl-morpholine.

2. Process according to claim 1, wherein M represents an alkali metal.
3. Process according to claim 1 or 2, wherein R^2 represents an alkyl group.
4. Process according to claim 3, wherein R^2 represents a t.-butyl group.
5. Process according to any one of claims 1-4, wherein the acid chloride forming agent is oxalylchloride.
6. Process according to any one of claims 1-5, wherein the acid chloride formation is performed in the presence of a catalyst.
7. Process according to any one of claims 1-6, wherein the amount of alcohol

with formula R^2OH is between 3 and 6 equivalents calculated with respect to the amount of salt with formula (2).

8. Process according to any one of claims 1-7, wherein first the salt with formula (2) is converted into the corresponding acid chloride and subsequently the acid chloride is contacted with the alcohol with formula R^2OH and N-methyl-morpholine.
9. Process according to claim 8, wherein the acid chloride is quenched with the alcohol with formula R^2OH and N-methyl-morpholine.
10. Process according to any one of claims 1-9, wherein R^1 represents a leaving group, and wherein the ester of formula 1 wherein R^1 represents a leaving group is subsequently converted into the corresponding ester with formula 1 wherein R1 represents an acyloxy group.
11. Process according to claim 10, wherein first an ester of formula 1 wherein R^1 represents an acyloxy group is prepared and subsequently the ester of formula 1 is converted into the corresponding compound with formula 1 wherein R^1 represents OH.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/NL 03/00435

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D319/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 06266 A (MINK DANIEL ;DSM NV (NL); KOOISTRA JACOB HERMANUS MATTHE (NL); MUL) 24 January 2002 (2002-01-24) page 5, line 4 -page 6, line 31; claim 8; example VII	1-11
A	WO 00 68221 A (EGYT GYOGYSZERVEGYESZETI GYAR ;VERECZKEYNE DONATH GYOERGYI (HU); B) 16 November 2000 (2000-11-16) page 7, paragraph 4	1-11
A	GB 885 516 A (ARTHUR HENRY CLARKSON) 28 December 1961 (1961-12-28) page 1: left-hand column, paragraph 4 page 2: right-hand column, last paragraph	1-11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 2003	12/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stroeter, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/NL 03/00435

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	MARCH J: "ALIPHATIC NUCLEOPHILIC SUBSTITUTION" ADVANCED ORGANIC CHEMISTRY. REACTIONS, MECHANISMS, AND STRUCTURE, NEW YORK, JOHN WILEY & SONS, US, 1992, page 392 XP002217003 ISBN: 0-471-60180-2 chapter 0-20 page 392 ---	1-11
A	MURPHY C F, KOEHLER R. E.: "CHEMISTRY OF CEPHALOSPORIN ANTIBIOTICS. XVIII." J. ORG. CHEM., vol. 35, no. 7, 1970, pages 2429-2430, XP002252465 right-hand column, first paragraph -----	1-11

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/NL 03/00435

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0206266 A	24-01-2002	NL 1015744 C2	22-01-2002
		AU 7583001 A	30-01-2002
		BR 0112535 A	01-07-2003
		CA 2415963 A1	24-01-2002
		CZ 20030163 A3	14-05-2003
		EP 1317440 A1	11-06-2003
		WO 0206266 A1	24-01-2002
		NO 20030025 A	03-01-2003
WO 0068221 A	16-11-2000	HU 9901526 A2	28-04-2001
		AU 4600200 A	21-11-2000
		CA 2373077 A1	16-11-2000
		CN 1349522 T	15-05-2002
		CZ 20013965 A3	17-04-2002
		EP 1178980 A1	13-02-2002
		HR 20010846 A1	28-02-2003
		WO 0068221 A1	16-11-2000
		JP 2002544207 T	24-12-2002
		PL 351145 A1	24-03-2003
		SK 15842001 A3	04-04-2002
GB 885516 A	28-12-1961	NONE	